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Anmelder/Applicant(s)/Demandeur(s):

Mallinckrodt Inc.
675 McDonnell Boulevard
St. Louis, MO 63134
ETATS-UNIS D'AMERIQUE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Labelling of vitamin B12 and derivatives thereof through the cyanide nitrogen in
[CO]-CN

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5 LABELLING OF VITAMIN B12 AND DERIVATIVES THEREOF THROUGH THE
CYANIDE NITROGEN IN [CO]-CN

The invention relates to the derivatization of
5 vitamin B12 for the labelling with radionuclides, mainly
 ^{111}In , $^{99\text{m}}\text{Tc}$ and ^{125}I . The invention further relates to the
resulting radiopharmaceuticals and their application as
radiodiagnostic or radiotherapeutic imaging.

Many patents and publications exists for the
10 derivatization of vitamin B12 at the corrin ring or the
ribose moiety.

It was found according to the invention that certain
metal complexes are able to coordinate directly to the
cyanide group in vitamin B12. It could be shown that this
15 type of binding is occurring in particular for the complex
[Tc(NO)(OH₂)(CO)₃] (NO = bidentate ligand) in which the
nitrogen atom of cyanide binds directly to the Tc metal
centre forming a [Co]-CN-Tc moiety. It is the first time that
a metal complex fragment is coordinating to the nitrogen in
20 [Co]-CN.

With the exception of the CN position, all other
sites in vitamin B12 are exhaustively claimed in patents for
labelling. To our knowledge, the cyanide is available since
nobody expected that it can act as a ligand group.

25 The invention thus relates to labeling of vitamin B12
with $^{99\text{m}}\text{Tc}$ for radiopharmaceutical application in e.g. cancer
diagnosis and therapy as well as coupling of other metal
fragments (e.g. Rh, Pt, Pd) to vitamin B12 through the
cyanide for stereospecific and/or enantioselective catalysis.

30 The reaction of vitamin B12 with low valent metal
complexes leads to the formation of a stable [Co]-CN-M
bridge. If M is $^{99\text{m}}\text{Tc}$, this is a convenient method of
labelling vitamin B12. If M is e.g. Rh(I) the corresponding

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complex can probably be used for catalysis since vitamin B12 provides a stereospecific sterical environment. If M is ^{99m}Tc or ^{188}Re then the precursor complex is typically $[\text{Tc}(\text{NO})(\text{OH}_2)(\text{CO})_3]$ in which OH_2 is substituted by Co-CN . The
5 ligand NO (or other donor combinations) is variable. This allows a systematic variation of the precursor complex and, thus, a straightforward possibility of product development by systematic structure-activity relationships. A good combination might then represent a labelled B12 derivative,
10 which is either an antagonist or an agonist for B12 receptors and/or transporters.

The ligand NO (or others) can also be bifunctional. One of the functions is used for coordination to the metal and the second function can additionally be coupled to e.g. a
15 targeting vector. This enables combination of receptor targeting, internalization and trapping of labelled vitamin B12. Such a derivative is also called a "trojan horse" if the additional functionality is e.g. enzymatically cleaved inside the cell. It releases then a functionally active or inactive
20 vitamine B12 compound.

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CLAIM

1. Method for labeling vitamin B12 with a metal,
comprising the reaction of vitamin B12 with a low valent
5 metal complex to obtain a stable [Co]-CN-M bridge.
2. Method as claimed in claim 1, wherein M is ^{99m}Tc or
 ^{188}Re .
3. Precursor complex having the general formula
[M(NO)(OH₂)(CO)₃] in which M is a low valent metal, in
10 particular ^{99m}Tc or ^{188}Re , OH₂ is substituted by Co-CN and the
ligand NO is variable.